

ORIGINAL ARTICLE

The Epidemiology of Childhood Cardiomyopathy in Australia

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ABSTRACT

BACKGROUND

The incidence and age distribution of primary cardiomyopathy in children are not well defined. We undertook a population-based, retrospective cohort study in Australia to document the epidemiology of childhood cardiomyopathy.

METHODS

We analyzed all cases of primary cardiomyopathy in children who presented between 1987 and 1996 and who were younger than 10 years of age. Children were recruited from multiple sources, and cases of cardiomyopathy were classified according to World Health Organization guidelines.

RESULTS

Over the 10-year period, 314 new cases of primary cardiomyopathy were identified, for an annual incidence of 1.24 per 100,000 children younger than 10 years of age (95 percent confidence interval, 1.11 to 1.38). Dilated cardiomyopathy made up 58.6 percent of cases, hypertrophic cardiomyopathy 25.5 percent, restrictive cardiomyopathy 2.5 percent, and left ventricular noncompaction 9.2 percent of cases. The incidence of all types of cardiomyopathy except restrictive declined rapidly after infancy. In 11 cases (3.5 percent), sudden death was the first symptom. There was a male predominance among children with hypertrophic and unclassified cardiomyopathy. Indigenous children had a higher incidence of dilated cardiomyopathy than nonindigenous children (relative risk, 2.67; 95 percent confidence interval, 1.42 to 4.63) and a higher rate of death as the presenting symptom (16.7 percent vs. 2.6 percent, $P=0.02$). Lymphocytic myocarditis was present in 25 of 62 children with dilated cardiomyopathy (40.3 percent) who underwent cardiac histologic examination within two months after presentation.

CONCLUSIONS

Lymphocytic myocarditis and left ventricular noncompaction are important causes of childhood cardiomyopathy in Australia. The timing and severity of presentation in children with cardiomyopathy are related to the type of cardiomyopathy, as well as to genetic and ethnic factors.

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THE PEDIATRIC CARDIOMYOPATHIES are an uncommon and heterogeneous group of disorders accounting for about half of all cardiac transplantations in children.¹ Studies of childhood cardiomyopathy usually reflect the experience at a single institution²⁻⁵ or in a single region.^{6,7} A better understanding of the epidemiology, causes, and outcomes of childhood cardiomyopathy would facilitate planning and provision of medical services.

The centralization of Australian pediatric tertiary services provides an opportunity to examine the incidence and natural history of rare conditions. This report describes epidemiologic observations from a retrospective, population-based cohort study of all Australian children who presented with cardiomyopathy over a 10-year period.

METHODS

SELECTION OF CHILDREN

The National Australian Childhood Cardiomyopathy Study includes all children with primary cardiomyopathy who presented between January 1, 1987, and December 31, 1996, and were younger than 10 years of age at presentation. The patients were enrolled by three primary investigators during a series of site visits to all 9 Australian pediatric cardiology centers and 12 additional hospitals caring for children with heart disease. Patients were sought from all Australian adult cardiologists, rural pediatricians, and cardiac transplantation centers. Ethics-committee approval was obtained according to the requirements for each center. At each location, study candidates were recruited from multiple sources, including cardiology and medical-record data bases and echocardiography log books.

The exclusion criteria included congenital heart disease; arrhythmia-induced cardiac dysfunction; Kawasaki's disease; prior exposure to corticosteroids or anthracyclines; a progressive systemic, metabolic, or neuromuscular disease resulting in other severe organ involvement; cardiac dysfunction resulting from abnormalities in other organs; and maternal diabetes or prematurity for children who presented before four weeks of age. The available medical records of each enrolled patient were reviewed, and prospective follow-up was arranged for patients who had not been seen within the preceding 12 months. Death was considered to be the presenting symptom in patients with sudden or unexplained death and no prior symptoms. Australian

law requires autopsies to be performed in cases of sudden or unexplained death, and these patients were identified from centralized records compiled by the Australian Bureau of Statistics, with the use of the same diagnostic codes used for hospital medical records.

CLASSIFICATION OF CASES

A single observer assigned each patient to a diagnostic category according to the World Health Organization's classification of cardiomyopathy,⁸ after directly reviewing all available cardiac information. Dilated cardiomyopathy was defined by reduced left ventricular systolic function in the presence of symptoms or a family history of dilated cardiomyopathy, a left ventricular fractional shortening of 20 percent or less in the absence of regional wall-motion abnormalities on echocardiography in asymptomatic patients without a family history, or typical pathological features at autopsy (including lymphocytic myocarditis). Hypertrophic cardiomyopathy was defined by otherwise unexplained septal hypertrophy, left ventricular free-wall hypertrophy, or both (wall thickness more than 2 SD above the normal mean), or a right ventricular free-wall thickness exceeding 4 mm. Restrictive cardiomyopathy was defined by impaired diastolic filling with preserved systolic function and normal ventricular-wall thickness. Unclassified cardiomyopathy comprised all other cases, including those with left ventricular noncompaction.⁹ Diagnostic features of left ventricular noncompaction included involvement of more than 50 percent of the affected left ventricular segment, based on cardiac imaging or direct examination of the heart. Echocardiographic measurements were normalized according to body-surface area.¹⁰ An example of an echocardiogram from a patient with left ventricular noncompaction is shown in Figure 1. Available cardiac histologic analyses from all sources were reviewed in a blinded fashion by a pediatric pathologist with cardiac expertise. Lymphocytic myocarditis was defined according to the Dallas criteria.¹¹ A diagnosis of familial cardiomyopathy required at least one affected first- or second-degree relative.

STATISTICAL ANALYSIS

Incidence rates were calculated with the use of the age-specific population at risk between 1987 and 1996.¹²⁻¹⁵ Ninety-five percent confidence intervals for incidence rates were calculated with the use of the Poisson distribution. Data were summarized as



Figure 1. Echocardiogram Showing Characteristic Features of Left Ventricular Noncompaction Involving the Left Ventricular Free Wall, Apex, and Lower Interventricular Septum.

Alternating finger-like myocardial trabeculations and deep myocardial recesses create a pseudohypertrophic spongiform appearance. RA denotes right atrium, LA left atrium, RV right ventricle, and LV left ventricle.

frequencies and percentages for categorical data and as medians for the age at presentation. Pearson's chi-square statistic or Fisher's exact test (when expected cell values were less than 5) was used to assess the association between two categorical variables. The Kruskal–Wallis rank-sum test (or the Mann–Whitney test for two groups) was used to compare the ages at presentation among the subgroups. Poisson regression was used to assess trends in the annual incidence of cardiomyopathy. Analyses were performed with the use of Stata software (version 6.0).¹⁶ All reported P values are two-sided.

RESULTS

During the 10-year study period, there were 314 new cases of cardiomyopathy: 184 cases of dilated cardiomyopathy (58.6 percent), 80 cases of hypertrophic cardiomyopathy (25.5 percent), 42 cases of unclassified cardiomyopathy (13.4 percent), and 8 cases of restrictive cardiomyopathy (2.5 percent). Of 42 children with unclassified cardiomyopathy, 29 had left ventricular noncompaction (9.2 percent of all cases), 9 had cardiac hypertrophy with initially impaired systolic function, 2 had familial neonatal cardiomyopathy that caused death within hours after delivery, 1 had oncocytic cardiomyopathy, and 1 had left ventricular dysfunction associated with a congenital left ventricular diverticulum.

INCIDENCE OF CARDIOMYOPATHY

Table 1 shows the annual incidence of each type of cardiomyopathy according to the age at presentation. The incidence of all types except restrictive cardiomyopathy declined markedly with age, with the highest annual incidence that of dilated cardiomyopathy before 12 months of age. There was little regional variation and no evidence of a change over time in the incidence of any type of cardiomyopathy ($P=0.88$).

PRESENTING SYMPTOMS

Death was the first manifestation of the disease (the presenting symptom) in 11 patients (3.5 percent), including 9 of 184 with dilated cardiomyopathy (4.9 percent), 2 of 42 with unclassified cardiomyopathy (4.8 percent), and none with hypertrophic or restrictive cardiomyopathy ($P=0.15$). Death as the presenting symptom was significantly more common among indigenous children (3 of 18, 16.7 percent) than among nonindigenous children (6 of 235, 2.6 percent) ($P=0.02$). There were 61 children whose ethnic origin was unknown, 2 of whom had death as the presenting symptom. Congestive heart failure was the presenting symptom in 165 of 184 children with dilated cardiomyopathy (89.7 percent), 6 of 80 with hypertrophic cardiomyopathy (7.5 percent), 4 of 8 with restrictive cardiomyopathy (50.0 percent), and 31 of 42 with unclassified cardiomyopathy (73.8 percent) ($P<0.001$).

AGE AT PRESENTATION

Figure 2 shows the cumulative frequency distribution of the age at presentation for each type of cardiomyopathy. The median age at presentation was 7.5 months among children with dilated cardiomyopathy, 5.7 months among those with hypertrophic cardiomyopathy, 3.8 months among those with unclassified cardiomyopathy, and 36.0 months among those with restrictive cardiomyopathy ($P=0.003$ for the overall comparison). In total, 63.4 percent of the patients presented before the age of 12 months.

SEX

The association between the type of cardiomyopathy and sex was significant ($P=0.001$ for the overall comparison). Of the 184 children with dilated cardiomyopathy, 103 were girls (56.0 percent), as were 25 of the 80 children with hypertrophic cardiomyopathy (31.2 percent), 4 of the 8 with restrictive cardiomyopathy (50.0 percent), and 16 of the 42 with unclassified cardiomyopathy (38.1 per-

Table 1. Annual Incidence of Each Type of Cardiomyopathy, According to the Age at Presentation.

Type of Cardiomyopathy	Age at Presentation				
	0 to <1 yr	1 to <2 yr	2 to <5 yr	5 to 10 yr	Total
Dilated					
No. of children	121	29	18	16	184
Annual incidence/100,000 children	4.76	1.14	0.24	0.13	0.73
95% Confidence interval	3.95–5.69	0.77–1.64	0.14–0.37	0.07–0.21	0.63–0.84
Hypertrophic					
No. of children	48	9	10	13	80
Annual incidence/100,000 children	1.89	0.36	0.13	0.10	0.32
95% Confidence interval	1.39–2.51	0.16–0.67	0.06–0.24	0.06–0.18	0.25–0.39
Restrictive					
No. of children	0	1	4	3	8
Annual incidence/100,000 children	0	0.04	0.05	0.02	0.03
95% Confidence interval	0–0.15	0–0.22	0.01–0.13	0.01–0.07	0.01–0.06
Unclassified					
No. of children	30	5	4	3	42
Annual incidence/100,000 children	1.18	0.20	0.05	0.02	0.17
95% Confidence interval	0.80–1.69	0.06–0.46	0.01–0.13	0.01–0.07	0.12–0.22
Total					
No. of children	199	44	36	35	314
Annual incidence/100,000 children	7.84	1.73	0.47	0.28	1.24
95% Confidence interval	6.79–9.00	1.26–2.33	0.33–0.65	0.19–0.39	1.11–1.38

cent). The last group included seven children with the Barth syndrome,¹⁷ an X-linked cardiomyopathy.

ETHNIC GROUP

Table 2 shows the incidence of each type of cardiomyopathy during the study period, according to ethnic background. Indigenous children had an annual incidence of dilated cardiomyopathy that was almost three times as high as that among non-indigenous children (1.52 vs. 0.57 per 100,000 children).

FAMILIAL CARDIOMYOPATHY

Familial cardiomyopathy was present in 19.7 percent of children. Table 3 shows the frequency of a family history of cardiomyopathy and the median age at presentation in each subgroup of children with cardiomyopathy. Children with dilated cardiomyopathy were less likely to have a family history of cardiomyopathy (27 of 184, 14.7 percent) than were those with either hypertrophic cardiomyopathy (19 of 80, 23.8 percent) or unclassified cardiomyopathy (15 of 42, 35.7 percent) ($P=0.01$). Children with familial dilated cardiomyopathy presented significantly earlier than those with nonfamilial dilated cardiomyopathy, and children with familial hyper-

trophic cardiomyopathy presented significantly later than those with nonfamilial hypertrophic cardiomyopathy.

PARENTAL CONSANGUINITY

As a potential marker of recessively inherited conditions, parental consanguinity was documented in 21 of 314 children (6.7 percent), and the parental consanguinity status was unknown in 33 of 314 (10.5 percent). Of those whose status was known, parental consanguinity was present in 14 of 160 with dilated cardiomyopathy (8.8 percent), 2 of 73 with hypertrophic cardiomyopathy (2.7 percent), and 5 of 40 with unclassified cardiomyopathy (12.5 percent) ($P=0.20$).

SYNDROMAL MALFORMATIONS

The most common underlying syndrome was Noonan's syndrome, present in 23 of 80 children with hypertrophic cardiomyopathy (28.8 percent). Two siblings with dilated cardiomyopathy had Leber's disease, and there was one case each of Costello's, Beckwith–Wiedemann, and Fukuyama's syndromes. Six children with multiple congenital extracardiac abnormalities (1.9 percent) had no definable syndrome.

METABOLIC AND MITOCHONDRIAL DISEASES

Of the 314 children, 28 (8.9 percent) had a metabolic disease etiologically linked to cardiomyopathy. These included a respiratory-chain enzyme deficiency in 10 children, the Barth syndrome in 8, a carnitine transporter defect in 4, and fatty-acid oxidation defects in 4. Seven of the eight children with the Barth syndrome had left ventricular noncompaction, and the eighth had dilated cardiomyopathy. The association between the type of cardiomyopathy and metabolic disease was significant, with 14 of 42 children with unclassified cardiomyopathy (33.3 percent) having a metabolic abnormality, as compared with 12 of 184 with dilated cardiomyopathy (6.5 percent) and 2 of 80 with hypertrophic cardiomyopathy (2.5 percent) ($P < 0.001$). Among the children with unclassified cardiomyopathy, 7 of 9 children with combined myocardial hypertrophy and systolic dysfunction at presentation (77.8 percent) had a metabolic abnormality, as did 7 of 29 with left ventricular noncompaction (24.1 percent). The age at presentation was unrelated to the presence of a metabolic abnormality.

LYMPHOCYTIC MYOCARDITIS

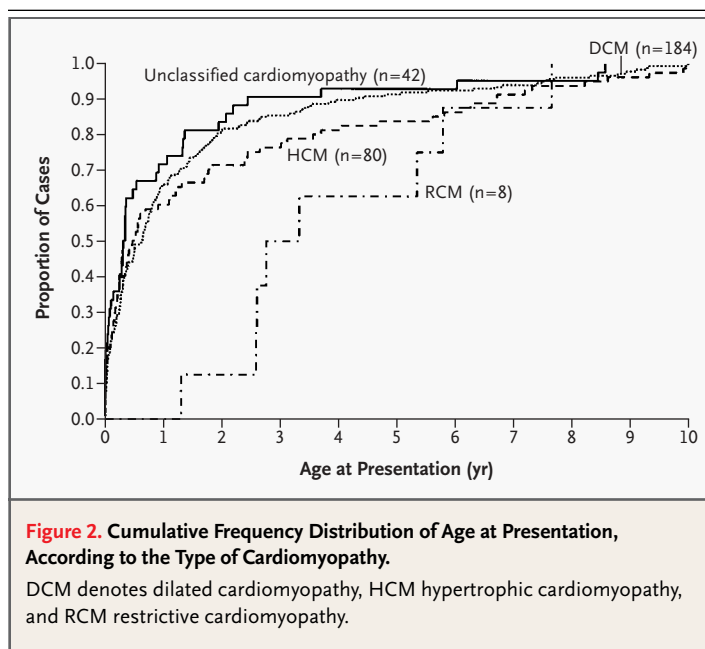
Lymphocytic myocarditis was present in 25 of 70 children with dilated cardiomyopathy who underwent cardiac histologic examination (35.7 percent), and in 25 of 62 children who underwent histologic examination within two months after presentation (40.3 percent).

Overall, one of the potential causes listed above was present in 66 of 184 children with dilated cardiomyopathy (35.9 percent), 44 of 80 with hypertrophic cardiomyopathy (55.0 percent), 1 of 8 with restrictive cardiomyopathy (12.5 percent), and 23 of 42 with unclassified cardiomyopathy (54.8 percent).

The proportion of children with dilated cardiomyopathy for which a potential cause was identified was significantly higher among those who underwent cardiac histologic examination within two months after presentation than among those who did not undergo histologic examination (36 of 62 children [58.1 percent] vs. 35 of 114 [30.7 percent], $P < 0.001$).

DISCUSSION

This study documents the incidence and presenting features of childhood cardiomyopathy in a national, population-based cohort. The acquisition of multicenter data was facilitated by the centralization of



pediatric specialty services, with 9 pediatric cardiology centers and 21 pediatric cardiologists serving a population of approximately 18 million people. The inclusion of data obtained at autopsy and from children seen by rural physicians and those treating adults ensured as far as possible that the study cohort was representative of the spectrum of children with cardiomyopathy. The uniformity of diagnostic criteria was ensured by having a single cardiologist systematically categorize the cases, reviewing all imaging information and using a single set of normal echocardiographic values. This may well account for the relatively high incidence—9.2 percent—of left ventricular noncompaction.

There are few published epidemiologic data on childhood cardiomyopathy. Among adults with hypertrophic cardiomyopathy, selection bias may skew outcomes and result in misconceptions about the severity of disease.¹⁸

In a population-based epidemiologic study of childhood cardiomyopathy in Finland,¹⁹ Arola et al. excluded patients with lymphocytic myocarditis and those who had spontaneous improvement within six months after presentation. Since post-viral cardiomyopathy may not be associated with lymphocytic myocarditis,²⁰ we recruited patients according to the findings at presentation, rather than on the basis of any outcome measure. Grenier et al. have described the North American Pediatric Cardiomy-

Table 2. Annual Incidence of Each Type of Cardiomyopathy According to Whether or Not the Children Were Indigenous.*

Type of Cardiomyopathy	Indigenous (N=18)		Nonindigenous (N=235)		Incidence Rate Ratio (95% CI)
	No. of Children	Annual Incidence/100,000 Children	No. of Children	Annual Incidence/100,000 Children	
Dilated	14	1.52	139	0.57	2.67 (1.42–4.63)
Hypertrophic	2	0.22	55	0.23	0.96 (0.11–3.65)
Restrictive	0	0	7	0.03	
Unclassified	2	0.22	34	0.14	1.57 (0.18–6.08)

* The ethnic background of 61 children was unknown. CI denotes confidence interval.

Table 3. Frequency of a Family History of Cardiomyopathy and Median Age at Presentation.*

Type of Cardiomyopathy	Total No. of Children	Family History	Median Age at Presentation		P Value†
			Family History	No Family History	
		no. (%)	mo		
Dilated	184	27 (14.7)	3.2	8.3	0.004
Hypertrophic	80	19 (23.8)	20.5	4.2	0.006
Restrictive	8	1 (12.5)	63.9	33.0	0.51
Unclassified	42	15 (35.7)	3.3	4.0	0.36
All types	314	62 (19.7)	5.8	6.9	—

* A diagnosis of familial cardiomyopathy required at least one affected first- or second-degree relative.

† The Mann–Whitney test was used to compare the median age at presentation according to the presence or absence of a family history.

opathy Registry,²¹ which includes children with progressive neuromuscular or multisystem metabolic diseases. In the North American²¹ and Finnish¹⁹ studies, the criteria for dilated cardiomyopathy included a left ventricular fractional shortening (or ejection fraction) that was less than 2 SD below the normal mean and a left ventricular dimension that was more than 2 SD above the normal mean. We used similar criteria for left ventricular systolic dysfunction in children with symptoms and those with

familial dilated cardiomyopathy, but we used a fractional shortening of 20 percent or less as a cutoff point in children with other types of dilated cardiomyopathy so as to minimize the inclusion of asymptomatic patients with borderline or mild left ventricular dysfunction of uncertain clinical significance. Because congestive heart failure is present in 90 percent of children with dilated cardiomyopathy,¹⁹ the number of children with sporadic cases who were excluded from our study was probably small.

In our study the annual incidence of cardiomyopathy was 1.24 per 100,000 children younger than 10 years of age. This parallels the incidence of 1.13 per 100,000 in the North American study, reported elsewhere in this issue of the *Journal*,²² but exceeds the incidence of 0.74 per 100,000 reported in the Finnish study.¹⁹ The exclusion of subjects with self-limiting cardiomyopathy from the Finnish study may explain these differences.

A closer comparison of the three studies can be made with respect to patients presenting before one year of age. For all types of cardiomyopathy, the annual incidence in our study was 7.84 per 100,000 children, as compared with 4.1 per 100,000 in Finland¹⁹ and 8.34 per 100,000 in North America.²² The annual incidence of dilated cardiomyopathy was 4.76 per 100,000 children, as compared with 3.8 per 100,000 in the Finnish study.¹⁹ Despite the use of similar inclusion criteria, the differences were more marked for infants with hypertrophic cardiomyopathy, with an annual incidence of 1.89 per 100,000 children in our study and 0.26 per 100,000 in the Finnish study.¹⁹

In our study, death was the presenting symptom in 4.9 percent of cases of dilated cardiomyopathy and 3.5 percent of all cases. In the Finnish study,¹⁹ 12 percent of cases were diagnosed at autopsy. Hypertrophic cardiomyopathy is the most common cause of sudden death from cardiac causes in healthy young adults,²³ but we found no cases of hypertrophic cardiomyopathy in which death was the presenting symptom. This probably reflects the young age of the study cohort.

Familial cardiomyopathy in our study was related to the age at presentation for both dilated and hypertrophic cardiomyopathy. Over 60 percent of the study population presented before one year of age, and the peak incidence of all types of cardiomyopathy except restrictive cardiomyopathy occurred before the age of three months. This finding is consistent throughout the regional studies^{6,7,24} and the larger epidemiologic studies.^{19,22} Dilated car-

diomyopathy due to lymphocytic myocarditis²⁵ and some cytoskeletal protein abnormalities²⁶ may develop early in life. In contrast, familial hypertrophic cardiomyopathy due to contractile protein abnormalities usually develops after the first decade.²⁷

Previous studies of cardiomyopathy^{19,24} have shown increasing rates of both dilated and hypertrophic cardiomyopathy in childhood, in contrast to our findings. Increasing rates of ascertainment might be explained by the increasing use of two-dimensional echocardiography since the early 1980s. Once indigenous or nonindigenous ethnic origin was taken into account, we found no significant regional differences in the Australian population.

We found a preponderance of boys among children with hypertrophic and unclassified cardiomyopathy (68.8 percent and 61.9 percent, respectively). The latter was largely accounted for by the presence of the Barth syndrome, an X-linked condition¹⁷ that was strongly associated with left ventricular non-compaction. Similar sex-based differences in hypertrophic cardiomyopathy were also reported in the Finnish¹⁹ and North American²² studies.

Despite the small numbers of indigenous children in our study, an increased risk of dilated cardiomyopathy was found in this group (relative risk, 2.67). Indigenous Australian children are also at increased risk for cardiovascular disease and death from rheumatic fever.²⁸ Ethnic differences in the incidence of cardiomyopathy were also found in the North American study.²² Both genetic and environmental factors may contribute to these differences. Decreased availability of health care among indigenous subjects may explain the higher rate of death as a presenting symptom in this group, but it could also have diluted the observed difference in the incidence of cardiomyopathy, owing to the lower rates of diagnosis.

A known or presumed cause was identified in 114 of 314 children (42.7 percent) in our study. Lymphocytic myocarditis was present in 40.3 percent of children with dilated cardiomyopathy who underwent cardiac histologic examination within two months after presentation, increasing the number of cases of dilated cardiomyopathy with a known or probable cause from 30.7 percent to 58.1 percent. These data confirm the importance of lymphocytic myocarditis as a cause of dilated cardiomyopathy in childhood. By comparison, only 10 percent of adults with dilated cardiomyopathy have lymphocytic myocarditis,²⁹ despite evidence of prior echovirus or

adenovirus infection, each in approximately 10 to 15 percent of cases.³⁰

Familial cardiomyopathy was ascertained in 19.8 percent of our study subjects and in 23 percent of those in the Finnish study.¹⁹ With prospective screening, the incidence of familial cardiomyopathy may have been even higher, owing to the inclusion of more subjects with latent cardiac dysfunction.³¹ Parental consanguinity, consistent with an autosomal recessive inheritance of cardiomyopathy, was documented in 6.7 percent of the children in our study. Advances in molecular genetics may identify the cause of autosomal recessively inherited cardiomyopathy.³²

Retrospective enrollment of patients may have led to incomplete case ascertainment. We attempted to minimize this possibility by using multiple data bases at each center, with the inclusion of patients seen by physicians who treat adults and by rural physicians, and examination of autopsy records. Subjects who were phenotypically negative but genotypically positive for cardiomyopathy were not included, since routine genetic testing was not available at the time of the study.

During the study period, advances in the diagnosis of genetic, infectious, and metabolic abnormalities were gradually incorporated into clinical protocols. Failure to perform all relevant investigations would have limited the diagnostic yield. However, the proportion of cases with an identified cause was at least similar to that in the prospective North American study.²²

This national population-based study documents the incidence and presenting features of childhood cardiomyopathy in Australia. The causes of childhood cardiomyopathy are diverse, and most cases are diagnosed in early infancy. As compared with nonindigenous children, indigenous Australian children have a higher incidence of dilated cardiomyopathy and a higher risk of death as the presenting symptom. In children with dilated cardiomyopathy, early cardiac histologic examination significantly increases the diagnostic yield. Left ventricular noncompaction is more common than previously recognized. The type of cardiomyopathy, as well as genetic and ethnic factors, determines the timing and severity of presentation of cardiomyopathy in childhood.

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APPENDIX

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